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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
SHIMIZU et al. :
Serial No. 09/403,429 : Group Art Unit 1615
Filed on October 20, 1999 : Examiner TRAN,S
For RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of Patent and Trademarks,
Washington, D.C.
Sir,

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 17-3,Aramaki aza Dobashi, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988 ;

That I have been employed by Takeda Chemical Industries, Ltd., Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Research Division of said company;

That I have been appointed Assistant Research Head of CNS pharmacology in said Pharmaceutical Research Division since 1997 ;

That I am a member of the Pharmaceutical Society of Japan.

That I am one of the co-inventors of the United States Patent Application Serial No. 09/403,429 filed on October 20, 1999;

That the following Experiment was conducted by myself and under my supervision and control:

EXPERIMENT

M thods

Production of ent ric coated granules

(1) Production of granules having a core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-400] was charged with 41.58 kg of Avicel SP crystaline cellulose;particle diameter of 100 to 200 μm) and with the inlet air temperature and the temperature of the load being controlled at 70 °C and about 31 °C respectively, a bulk liquid of the following composition was coated on the Avicel by the tangential spray method at a spray rate of 1400g/min. The spraying operation was stopped when the specified amount (244.2 kg) of the bulk liquid has been delivered.

Bulk liquid:

Lansoprazole	39.6 kg
Magnesium carbonate	13.2 kg
Low-substituted hydroxypropyl cellulose	6.6 kg
Hydroxypropyl cellulose (Type SSL)	13.2 kg
Water	171.6 kg

(2) Production of film-undercoated granules having a core

Following this with the inlet air temperature and the temperature of the loading being controlled at 77 °C and about 41 °C, respectively, an undercoating liquid of the following composition was applied by the tangential spray method at a spray rate of 1200 g /min. The spraying operation was stopped when the specified amount (165.k0 g) of the undercoating liquid has been delivered and the load was dried in the granulator for 10 minutes. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #100 circular sieve (150 μm) to provide 120 kg of film-undercoated granules having a core. The average particle diameter of the obtained granules was 233μm.

Undercoating liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	9.24 kg
Titanium oxide	3.96 kg
Talc	3.96 kg
Low-substituted hydroxypropyl cellulose	6.60 kg

Mannitol	9.24 kg
Water	132.0 kg

(3) Production of enteric coated granules having a core

The same fluidized coating granulator (MP-400) was charged with 44.0 kg of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 85 °C and about 41 °C, respectively, an enteric film coating liquid(A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 1050 g /min. The specified amount 54.6kg of the enteric film coating liquid(A) had been sprayed.

Enteric film coating liquid(A):

Eudragit L30D-55	32.050 kg
Eudragit NE30D	3.570 kg
Polyethylene glycol 8000	1.071 kg
citric acid anhydrous	0.0126 kg
Glyceryl monostearate	0.630 kg
Polysorbate 80	0.189 kg
Ferric oxide	0.0063 kg
Ferric oxide(yellow)	0.0063 kg
Water	44.37 kg

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80 °C and about 41 °C, respectively, an enteric film coating liquid(B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 1050 g /min. The specified amount 201.6kg of the enteric film coating liquid(B) had been sprayed.

Enteric film coating liquid(B):

Eudragit L30D-55	117.600 kg
Eudragit NE30D	13.060 kg
Triethyl citrate	7.850 kg
citric acid anhydrous	0.021 kg

Glyceryl monostearate	2.520 kg
Polysorbate 80	0.756 kg
Ferric oxide	0.0252 kg
Ferric oxide(yellow)	0.0252 kg
Water	59.74 kg

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80 °C and about 41 °C, respectively, the enteric film coating liquid(A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 1050 g /min. The specified amount 27.3kg of the enteric film coating liquid(A) had been sprayed.

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80 °C and about 41 °C, respectively, a film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 1050 g /min. The spraying operation was stopped when the specified amount (29.4 kg) of the film coating liquid has been delivered and then drying was carried out in the granulator for 11 minutes. The resulting granules were sieved through a #35 circular sieve (425 μm) and a #60 circular sieve (250 μm) to provide 100.3 kg of enteric coated granules having a core.
The average particle diameter of the obtained granules was 330μm.

Film coating liquid:

Mannitol	4.20 kg
Water	25.20 kg

Example A(Production of orally disintegrable tablets using L-HPC(the content of hydroxypropoxyl group is within 5.0 to 7.0%)

(1) Production of erythritol-granulated powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 484 g of erythritol

[manufactured by Nikken Chemical Co., Ltd. (Japan)], 90g of low-substitutedhydroxypropyl cellulose LH-33(hydroxypropyl group contents : 5.8 weight %), 18g of microcrystalline cellulose [CEOLUS KG-801(trade name), manufactured by Asahi Chemical Co.,Ltd.(Japan)], 6g of citric acid anhydrous and granulation was carried out while spraying 300 g of purified water. The granules were dried to provide 566.3 g of granulated powders.

(2) Production of mixed powders

To 448.5 g of the above erythritol-granulated powders were added 270 g of the above enteric coated granules having a core, and 1.5 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(3) Production of orally disintegrable tablets

720 g of the above mixed powders were tabletted using a rotary type tabletting machine with a punch beveled edge), 10 mm in diameter, at a tabletting pressure of 26 KN/punch, to provide tablets each weighing 360 mg.

Example B(Production of orally disintegrable tablets using L-HPC(the content of hydroxypropoxyl group is 7.1% or over)

(1) Production of erythritol-granulated powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 484 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 90g of low-substitutedhydroxypropyl cellulose LH-31(hydroxypropyl group contents : 11.8 weight %), 18g of microcrystalline cellulose [CEOLUS KG-801(trade name), manufactured by Asahi Chemical Co.,Ltd.(Japan)], 6g of citric acid anhydrous and granulation was carried out while spraying 300 g of purified water. The granules were dried to provide 596.6 g of granulated powders.

(2) Production of mixed powders

To 448.5 g of the above erythritol-granulated powders were added 270 g of the above enteric coated granules having a core,

and 1.5 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(3) Production of orally disintegrable tablets

720 g of the above mixed powders were tabletted using a rotary type tabletting machine with a punch (beveled edge), 10 mm in diameter, at a tabletting pressure of 26 KN/punch, to provide tablets each weighing 360 mg.

Average particle diameter: Volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution)

Determination was carried out with Laser Diffraction Analyzer, type: HEROS RODOS [trade name, manufactured by Sympatec (Germany)].

(1) Hardness test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd. (Japan)]. The test was performed in 10 runs and mean values were shown.

(2) Oral disintegration time and acceptability of mouth feel

Oral disintegration time was determined by a panel of two male and two female. The panels put each one tablet on their tongue and measure the time until the tablet was disintegrated without chewing the tablet. The mouth feel was recorded as chalky, slightly chalky or not chalky.

Results

The results of the hardness, oral disintegration time and acceptability of mouth feel obtained in Example A and Example B are as follows.

	Ex. A	Ex. B
Hardness	27.3 N	25.6 N
Oral disintegration time		0.1 - 1 min.
Average	29 s	54 s
min - max	22-36 s	46-63 s
Mouth feel	Rapidly dissolved in the oral cavity	Less rapidly dissolved in the oral cavity
	·No chalky taste	·A little chalky taste

Conclusion

As is clear from the above results, the tablet obtained in Example A(orally disintegrable tablets using L-HPC(the content of hydroxypropoxyl group is within 5.0 to 7.0%)) and Example B (orally disintegrable tablets using L-HPC(the content of hydroxypropoxyl group is 7.1% or over)) have suitable strengths.

The tablet obtained in Example A (orally disintegrable tablets using L-HPC(the content of hydroxypropoxyl group is within 5.0 to 7.0%)) has superior to to the tablet obtained in Example B (the content of hydroxypropoxyl group is 7.1% or over)) in oral disintegration time and mouth feel.

It is declared by the undersigned that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 6th day of April, 2001.

Toshihiro Shimizu

Toshihiro SHIMIZU